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(54) Title: BETA-CHEMOKINE, H1305 (MCP-2)

(57) Abstract

Polynucleotides encoding H1305 and related proteins are disclosed. H1305 proteins and methods for their production are also disclosed.

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# BETA-CHEMOKINE, H1305 (MCP-2)

## Field of the Invention

The present invention relates to H1305 proteins, nucleic acids encoding such proteins, and methods of treatment using such proteins.

## Background of the Invention

Chemokines are a subclass of cytokines which cause the directed migration or chemotaxis of particular cell populations either to or away from higher concentrations of the chemokine. Many chemokines have been identified which cause migration of major blood cell populations. These factors may be useful for directing the migration of cell populations to areas of desired action or away from areas of unwanted action. It would, therefore, be desirable to identify new chemokines and polynucleotides encoding them.

## Summary of the Invention

In developing the present invention, methods were employed which selectively identify polynucleotides which encode secreted proteins. One such polynucleotide was isolated which encodes "H1305." In accordance with the present invention, polynucleotides encoding H1305 and active fragments thereof are disclosed. "H1305" is used throughout the present specification to refer to both proteins and polynucleotides encoding those proteins and to refer to proteins and polynucleotides from all mammalian species.

In certain embodiments, the present invention provides an isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of:

(a) the nucleotide sequence of SEQ ID NO:1 from nucleotide 47 to nucleotide 373;

(b) a nucleotide sequence capable of hybridizing to a nucleic acid sequence specified in (a);

(c) a nucleotide sequence varying from the sequence of the nucleotide sequence specified in (a) as a result of degeneracy of the genetic code;

(d) a nucleotide sequence encoding a fragment of the amino acid sequence of SEQ ID NO:2; and

(e) an allelic variant of the nucleotide sequence specified in (a).

Polynucleotides comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 47 to nucleotide 373 are particularly preferred. Preferably, the polynucleotide of the invention encodes a protein having H1305 activity. In other embodiments the polynucleotide is operably linked to an expression control sequence.

Host cells transformed with the polynucleotides of the invention are also provided. including mammalian cells.

Processes are also provided for producing a H1305 protein, said processes comprising:

(a) growing a culture of the host cell of the invention in a suitable culture medium; and

(b) purifying the H1305 protein from the culture.

Isolated H1305 protein is also provided which comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:2; and

(b) fragments of (a) having H1305 activity.

Proteins comprising the amino acid sequence of SEQ ID NO:2 are particularly preferred. Preferably, the protein has H1305 activity. Pharmaceuticals composition comprising a H1305 protein of the invention and a pharmaceutically acceptable carrier are also provided.

Compositions are also disclosed which comprise an antibody which specifically reacts with a H1305 protein of the invention.

Methods of treating a mammalian subject are also provided which comprise administering a therapeutically effective amount of a pharmaceutical composition comprising a H1305 protein.

Detailed Description of Preferred Embodiments

The inventors of the present application have identified and provided a polynucleotide encoding a H1305 protein. SEQ ID NO:1 provides the nucleotide sequence of a cDNA encoding the H1305 protein. SEQ ID NO:2 provides the amino acid sequence of the H1305 protein predicted from the DNA coding sequence. The amino acid sequence of H1305 contains known chemokine sequence motifs and shows homology with known chemokines.

Forms of H1305 protein of less than full length are encompassed within the present invention and may be produced by expressing a corresponding fragment of the polynucleotide encoding the H1305 protein (SEQ ID NO:1). These corresponding polynucleotide fragments are also part of the present invention. Modified polynucleotides as described above may be made by standard molecular biology techniques. including site-directed mutagenesis methods which are known in the art or by the polymerase chain reaction using appropriate oligonucleotide primers. A mature form of the H1305 protein, if it differs from the full-length sequence of SEQ ID NO:2, can be produced by expression of the full-length polynucleotide in an appropriate cell line.

For the purposes of the present invention, a protein has "H1305 activity" if it either (1) displays chemoattractant or chemotactic activity in a chemoattraction or chemotaxis assay (preferably an assay in which the corresponding species full-length H1305 is active), or (2) displays biological activity in a factor-dependent cell proliferation assay (preferably an assay in which the corresponding species full-length H1305 is active), or (3) displays activity in the induction of lymphokine production or effector function in an immune cell functional assay. Examples of effector function include, without limitation, tumoricidal activity, granule release, adhesion molecule expression, and the like. Activity may be monitored using assays known in the art. Chemoattractant or chemotactic activity can also be measured *in vivo* by injecting protein at a particular site and performing a histological examination of the cell types that migrate to the site of injection.

H1305 protein or fragments thereof having H1305 activity may be fused to carrier molecules such as immunoglobulins. For example, H1305 protein may be fused through "linker" sequences to the Fc portion of an immunoglobulin.

The invention also encompasses allelic variations of the nucleotide sequence as set forth in SEQ ID NO:1, that is, naturally-occurring alternative forms of the isolated polynucleotide of SEQ ID NO:1 which also encode H1305 or H1305 proteins having H1305 activity. Also included in the invention are isolated polynucleotides which hybridize to the nucleotide sequence set forth in SEQ ID NO:1 under highly stringent (e.g., 0.2xSSC at 65°C). stringent (e.g. 4xSSC at 65°C or 50% formamide and 4xSSC at 42°C), or relaxed (e.g., 4xSSC at 50°C or 30-40% formamide and 4xSSC at 42°C) conditions. Isolated polynucleotides which encode H1305 protein but which differ from the nucleotide sequence set forth in SEQ ID NO:1 by virtue of the degeneracy of the genetic code are also encompassed by the present invention. Variations in the nucleotide sequence as set forth in SEQ ID NO:1 which are caused by point mutations or by induced modifications which enhance H1305 activity, half-life or production level are also included in the invention.

Polynucleotides encoding H1305 proteins of other animal species, particularly mammalian species, can be obtained by using portions of SEQ ID NO:1 as a probe of a DNA library made from appropriate sources for such other species.

The isolated polynucleotides of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman et al., Nucleic Acids Res. 19, 4485-4490 (1991), in order to produce the H1305 protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, Methods in Enzymology 185, 537-566 (1990). As defined herein "operably linked" means enzymatically or chemically ligated to form a covalent bond between the isolated polynucleotide of the invention and the expression control sequence, in such a way that the H1305 protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

A number of types of cells may act as suitable host cells for expression of the H1305 protein. Any cell type capable of expressing functional H1305 protein may be used. Suitable mammalian host cells include, for example, monkey COS

cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from in vitro culture of primary tissue, primary explants. HeLa cells, mouse L cells, BHK, HL-60, U937, HaK, Rat2, BaF3, 32D, FDCP-1, PC12 or C2C12 cells.

The H1305 protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, e.g., Invitrogen, San Diego, California, U.S.A. (the MaxBac® kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference.

Alternatively, the H1305 protein may be produced in lower eukaryotes such as yeast or in prokaryotes such as bacteria. Suitable yeast strains include Saccharomyces cerevisiae, Schizosaccharomyces pombe, Kluyveromyces strains, *Candida*, or any yeast strain capable of expressing heterologous proteins. Suitable bacterial strains include *Escherichia coli*, *Bacillus subtilis*, *Salmonella typhimurium*, or any bacterial strain capable of expressing heterologous proteins.

The H1305 protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a polynucleotide sequence encoding the H1305 protein.

The H1305 protein of the invention may be prepared by growing a culture of transformed host cells under culture conditions necessary to express the desired protein. The resulting expressed protein may then be purified from the culture medium or cell extracts. The H1305 protein of the invention can be purified from conditioned media.

The H1305 protein can be purified using methods known to those skilled in the art. For example, the H1305 protein of the invention can be concentrated using a commercially available protein concentration filter, for example, an Amicon or Millipore Pellicon ultrafiltration unit. Following the concentration

step, the concentrate can be applied to a purification matrix such as a gel filtration medium. Alternatively, an anion exchange resin can be employed, for example, a matrix or substrate having pendant diethylaminoethyl (DEAE) groups. The matrices can be acrylamide, agarose, dextran, cellulose or other types commonly employed in protein purification. Alternatively, a cation exchange step can be employed. Suitable cation exchangers include various insoluble matrices comprising sulfopropyl or carboxymethyl groups. Sulfopropyl groups are preferred (e.g., S-Sepharose® columns). The purification of the H1305 protein from culture supernatant may also include one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearl® or Cibacrom blue 3GA Sepharose®; or by hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or by immunoaffinity chromatography. Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant methyl or other aliphatic groups, can be employed to further purify the H1305 protein. Some or all of the foregoing purification steps, in various combinations or with other known methods, can also be employed to provide a substantially purified isolated recombinant protein.

Preferably, the H1305 protein is purified so that it is substantially free of other mammalian proteins.

It is believed that H1305, active fragments and variants thereof, and H1305 related proteins (collectively "H1305 proteins") possess chemokine activities. Therefore, H1305 and H1305 related proteins may have an effect on chemotaxis or migration of blood cells, including without limitation eosinophils, basophils, dendritic cells, natural killer cells, neutrophils, monocytes, T cells and mast cells. A protein or peptide has "chemotactic activity," as used herein, if it can stimulate, directly or indirectly, the directed orientation or movement of cells, including myeloid and lymphoid cells. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein or peptide has chemotactic activity for cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

H1305 proteins may also be useful for inhibition of viral replication, including without limitation replication of HIV.

Isolated H1305 proteins, purified from cells or recombinantly produced, may be used as a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may contain, in addition to H1305 protein and carrier, diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11. IL-12, IL-13, IL-14, IL-15, G-CSF, γ-IFN, stem cell factor, and erythropoietin. The pharmaceutical composition may contain thrombolytic or anti-thrombotic factors such as plasminogen activator and Factor VIII. The pharmaceutical composition may further contain other anti-inflammatory agents. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with H1305 protein, or to minimize side effects caused by the H1305 protein. Conversely, H1305 protein may be included in formulations of the particular cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent.

The pharmaceutical composition of the invention may be in the form of a liposome in which H1305 protein is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers which in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for

example, in U.S. Patent No. 4.235,871; U.S. Patent No. 4.501,728; U.S. Patent No. 4.837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, e.g., amelioration of symptoms of, healing of, or increase in rate of healing of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of H1305 protein is administered to a mammal. H1305 protein may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines, other hematopoietic factors or vaccine components (such as antigens or other adjuvants), H1305 protein may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering H1305 protein in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

Administration of H1305 protein used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, or cutaneous, subcutaneous, or intravenous injection. Intravenous administration to the patient is preferred.

When a therapeutically effective amount of H1305 protein is administered orally, H1305 protein will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the

invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% H1305 protein, and preferably from about 25 to 90% H1305 protein. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of H1305 protein, and preferably from about 1 to 50% H1305 protein.

When a therapeutically effective amount of H1305 protein is administered by intravenous, cutaneous or subcutaneous injection, H1305 protein will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to H1305 protein an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additive known to those of skill in the art.

The amount of H1305 protein in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of H1305 protein with which to treat each individual patient. Initially, the attending physician will administer low doses of H1305 protein and observe the patient's response. Larger doses of H1305 protein may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not generally increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.1 $\mu$g to about

100 mg of H1305 protein per kg body weight, preferably about 0.1 μg to about 10 mg of H1305 protein per kg body weight, more preferably about 0.1 μg to about 100 μg of H1305 protein per kg body weight, most preferably about 0.1 μg to about 10 μg of H1305 protein per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of the H1305 protein will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

H1305 proteins may also be useful for treatment of wounds. In such applications, the protein may be administered as described above, if appropriate, or may be applied in other suitable forms, such as by topical administration in the form of a solution, suspension, ointment, salve, compress and the like.

H1305 protein of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the H1305 protein and which may inhibit H1305 binding to its receptor. Such antibodies are also useful for performing diagnostics assays for H1305 in accordance with known methods. Such antibodies may be obtained using the entire H1305 protein as an immunogen, or by using fragments of H1305 protein. The peptide immunogens additionally may contain a cysteine residue at the carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Additional peptide immunogens may be generated by replacing tyrosine residues with sulfated tyrosine residues. Methods for synthesizing such peptides are known in the art, for example, as in R.P. Merrifield, J.Amer.Chem.Soc. 85, 2149-2154 (1963); J.L. Krstenansky, et al., FEBS Lett. 211, 10 (1987).

Neutralizing or non-neutralizing antibodies (preferably monoclonal antibodies) binding to H1305 protein may also be useful therapeutics for certain tumors and also in the treatment of conditions described above. These neutralizing

monoclonal antibodies are capable of blocking the ligand binding to the H1305 protein or may promote clearance of protein from the patient.

## Example

### Isolation of H1305 cDNA

A partial clone for H1305 was isolated from a cDNA library made from RNA isolated from stimulated human peripheral blood mononuclear cells using methods which are selective for secreted proteins. Sequence from this partial clone was then used to identify a full-length clone from a PBMC library. Comparison of this sequence to the sequence of the original partial clone confirmed identity and that the isolated cDNA was full-length. The full-length clone (H1305, SEQ ID NO:1) was deposited with the American Type Culture Collection on December 13, 1995 and assigned accession number ATCC 69968.

All patent and literature references cited herein are incorporated by reference as if fully set forth.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Racie, Lisa A.
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McCoy, John

(ii) TITLE OF INVENTION: Chemokine H1305

(iii) NUMBER OF SEQUENCES: 2

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(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:
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(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
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(B) REGISTRATION NUMBER: 32,724
(C) REFERENCE/DOCKET NUMBER: GI5265

(ix) TELECOMMUNICATION INFORMATION:
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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 411 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 47..373

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

GAATTCGGCC AAAGAGGCTA GAACAACCCA GAAACCTTCA CCTCTC ATG CTG AAG 55
Met Leu Lys
1

```
CTC ACA CCC TTG CCC TCC AAG ATG AAG GTT TCT GCA GCG CTT CTG TGC      103
Leu Thr Pro Leu Pro Ser Lys Met Lys Val Ser Ala Ala Leu Leu Cys
  5                  10                  15

CTG CTG CTC ATG GCA GCC ACT TTC AGC CCT CAG GGA CTT GCT CAG CCA      151
Leu Leu Leu Met Ala Ala Thr Phe Ser Pro Gln Gly Leu Ala Gln Pro
 20                  25                  30                  35

GAT TCA GTT TCC ATT CCA ATC ACC TGC TGC TTT AAC GTG ATC AAT AGG      199
Asp Ser Val Ser Ile Pro Ile Thr Cys Cys Phe Asn Val Ile Asn Arg
             40                  45                  50

AAA ATT CCT ATC CAG AGG CTG GAG AGC TAC ACA AGA ATC ACC AAC ATC      247
Lys Ile Pro Ile Gln Arg Leu Glu Ser Tyr Thr Arg Ile Thr Asn Ile
         55                  60                  65

CAA TGT CCC AAG GAA GCT GTG ATC TTC AAG ACC CAA CGG GGC AAG GAG      295
Gln Cys Pro Lys Glu Ala Val Ile Phe Lys Thr Gln Arg Gly Lys Glu
     70                  75                  80

GTC TGT GCT GAC CCC AAG GAG AGA TGG GTC AGG GAT TCC ATG AAG CAT      343
Val Cys Ala Asp Pro Lys Glu Arg Trp Val Arg Asp Ser Met Lys His
 85                  90                  95

CTG GAC CAA ATA TTT CAA AAT CTG AAG CCA TGAGCCTTCA TACATGGACT       393
Leu Asp Gln Ile Phe Gln Asn Leu Lys Pro
100                 105

GAGAGTCAGA GCTTGAAG                                                411
```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 109 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```
Met Leu Lys Leu Thr Pro Leu Pro Ser Lys Met Lys Val Ser Ala Ala
  1               5                  10                  15

Leu Leu Cys Leu Leu Leu Met Ala Ala Thr Phe Ser Pro Gln Gly Leu
             20                  25                  30

Ala Gln Pro Asp Ser Val Ser Ile Pro Ile Thr Cys Cys Phe Asn Val
         35                  40                  45

Ile Asn Arg Lys Ile Pro Ile Gln Arg Leu Glu Ser Tyr Thr Arg Ile
     50                  55                  60

Thr Asn Ile Gln Cys Pro Lys Glu Ala Val Ile Phe Lys Thr Gln Arg
 65                  70                  75                  80

Gly Lys Glu Val Cys Ala Asp Pro Lys Glu Arg Trp Val Arg Asp Ser
                 85                  90                  95

Met Lys His Leu Asp Gln Ile Phe Gln Asn Leu Lys Pro
            100                 105
```

What is claimed is:

1. An isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of:

(a) the nucleotide sequence of SEQ ID NO:1 from nucleotide 47 to nucleotide 373;

(b) a nucleotide sequence capable of hybridizing to a nucleic acid sequence specified in (a);

(c) a nucleotide sequence varying from the sequence of the nucleotide sequence specified in (a) as a result of degeneracy of the genetic code;

(d) a nucleotide sequence encoding a fragment of the amino acid sequence of SEQ ID NO:2; and

(e) an allelic variant of the nucleotide sequence specified in (a).

2. The polynucleotide of claim 1 wherein said nucleotide sequence encodes a protein having H1305 activity.

3. The polynucleotide of claim 1 wherein said nucleotide sequence is operably linked to an expression control sequence.

4. The polynucleotide of claim 1 comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 47 to nucleotide 373.

5. A host cell transformed with the polynucleotide of claim 3.

6. The host cell of claim 5, wherein said cell is a mammalian cell.

7. A process for producing a H1305 protein, said process comprising:

(a) growing a culture of the host cell of claim 5 in a suitable culture medium; and

(b) purifying the H1305 protein from the culture.

8. An isolated H1305 protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:2; and

(b) fragments of (a) having H1305 activity.

9. The protein of claim 8 comprising the amino acid sequence of SEQ ID NO:2.

10. A pharmaceutical composition comprising a H1305 protein of claim 8 and a pharmaceutically acceptable carrier.

11. A H1305 protein produced according to the process of claim 7.

12. A composition comprising an antibody which specifically reacts with a H1305 protein of claim 8.

13. A method of treating a mammalian subject comprising administering a therapeutically effective amount of a composition of claim 10.

# INTERNATIONAL SEARCH REPORT

International Application No
PC[illegible]/US 97/00379

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/19 C07K14/52 A61K38/19 C07K16/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | INTERNATIONAL IMMUNOLOGY, vol. 1, 1989, pages 388-399, XP000673182 CHANG, H. ET AL.: "Cloning and expression of a gamma-interferon-inducible gene in monocytes: a new member of a cytokine gene family" see figure 7 --- | 1-3,5,7, 8,11 |
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[X] Further documents are listed in the continuation of box C.

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| Name and mailing address of the ISA<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax (+31-70) 340-3016 | Authorized officer<br>Andres, S |

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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| X | JOURNAL OF EXPERIMENTAL MEDICINE, vol. 176, July 1992, pages 59-65, XP000673185 VAN DAMME, J. ET AL.: "Structural and functional identification of two human, tumor-derived monocyte chemotactic proteins (MCP-2 and MCP-3) belonginig to the chemokine family" see figure 3 --- | 8,11,12 |
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Information on patent family members

International Application No
PCT/US 97/00379

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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